REMARKS

The undersigned thanks Examiners Salmon and Shukla for the courtesies extended during the interviews of June 13, 2007, and July 20, 2007. Applicants agree with the Interview Summaries of these interviews.

During the interview of July 20, 2007, the Examiners agreed that neither Cao nor Mirkin disclose "at least one of the Raman-active oligonucleotide probes comprises a *positively charged* Raman signal enhancer" and "aggregating *pre-made* metallic colloid or aggregate of nanoparticles with said at least one of the Raman active oligonucleotide probes comprising the positively charged Raman signal enhancer" which are recited in claims 1 and 41, respectively. The undersigned explained that metallic colloids or nanoparticles can be pre-made or synthesized in situ as explained in paragraph [0050] of the specification. Cao teaches Ag nanoparticles that are synthesized in situ, *not* pre-made. On the other hand, independent claim 22 and dependent claims 41 and 42 are limited to pre-made metallic colloids. The Examiners also proposed claim language such that the claim language would conform to the specification. Applicants sincerely appreciate these suggestions of the Examiners and have adopted them in preparing this Amendment.

Claims 1, 22 and 33 have been amended to distinguish over the prior art. These amendment are fully supported by Figure 2, which is described in paragraph [0050] of the specification. Claim 1 recites the additional limitation "wherein at least one of the Raman-active oligonucleotide probes comprises a positively charged Raman signal enhancer." Figure 2 shows Raman-active oligonucleotide probes 40 (paragraph [0050], lines 1-2) having a positively charged enhancer 60 (paragraph [0050], lines 3 and 4). Claims 22, 41 and 42 recite "aggregating [or applying] pre-made metallic colloid or aggregate of nanoparticles." This limitation is supported by paragraph [0050], lines 7-10, of the specification, which states "silver colloids or nano-particles can be aggregated with the oligonucleotides ... [and that the] metal colloids can be pre-made ... .").
Note the metallic colloids or nanoparticles are not limited to those containing silver or just a metal as there is ample support throughout the specification that the metallic colloids can include "suitable Raman-active organic compound" (see paragraph [0032]) or that the metallic colloids could include

two different metals from among "silver, gold, platinum, aluminum, and the like" (see paragraph [0033]).

Also, the newly added limitation recited in claim 33 is supported by Figure 2 as explained above in the context of the newly added limitation recited in claim 1.

New claims 38-40 are fully supported by Figure 4b, sample GTMN, wherein the tag "AmC6" is in the backbone of the oligonucleotide probe. Claim 44 is supported by paragraph [0050] of the specification.

Claim Rejection - 35 U.S.C. §103

Claims 1-7, 9-10, 13-17 were rejected as being obvious over Cao in view of Mirkin. This rejection is respectfully traversed.

Please note the following features of Cao: (1) the Raman-active tag, which is *not* positively charged, is attached to the Au nanoparticle, not to an oligonucleotide probe (see page 1537, first column, lines 33-36), and (2) the tag's signal is enhanced by *in-situ* aggregating Ag nanoparticles around the Au nanoparticle (see page 1537, first column, lines 6-10, from the bottom, and page 1537, middle column, lines 9-12, which states, "Before Ag enhancing, the nanoparticle probes were invisible to the naked eye, and no Raman scattering signal was detectable (Fig. 1A)."). In short, Cao does *not* use either a positively charged tag or pre-made metallic colloids or aggregate of nanoparticles. On the contrary, the embodiments of the present invention use oligonucleotide probes comprising a *positively charged* Raman signal enhancer as recited in claim 1 while, as explained above, the Raman tag of Cao not positively charged and is attached to the Au nanoparticle, not the oligonucleotide probe. Furthermore, some embodiments of the method of the present invention use *pre-made* aggregate of metallic colloids or nanoparticles as recited in claims 22, 41 and 42 while Cao's method synthesizes the Ag nanoparticles in-situ around the Au nanoparticle having the Raman tag thereon. Also, other embodiments of the present invention use a

Raman tag attached to the *backbone* of the oligonucleotide probe or nucleic acid as recited in claims 38-40 while the tag in Cao is attached to the Au nanoparticle.

Furthermore, even if Cao would have been combined with Mirkin, one of ordinary skill in this art would not have arrived at the embodiments of invention of claims 1-7, 9-10, 13-17. If Cao would have been modified as taught by Mirkin in column 58, lines 42-44, then the amine of the amino-modifier of Mirkin would *inevitably* be used to attached the Raman tag of Mirkin to the Au nanoparticle according to Mirkin. In this case, there would be *no* positively charged group such as a primary amine left as the amine would be linking the Au nanoparticle to the Raman tag. The Examiner has acknowledged that Cao fails to disclose "attaching a primary amine Raman signal enhancer" on page 5, lines 7-8, from the bottom. The Examiner believes that Mirkin fills this gap. However, as explained above, the combination of Cao and Mirkin would still *not* result in "at least one of the Raman-active oligonucleotide probes comprises a positively charged Raman signal enhancer" as recited in claim 1.

In short, both Cao and Mirkin fail to disclose "at least one of the Raman-active oligonucleotide probes comprises a positively charged Raman signal enhancer" as recited in claim 1, and "aggregating [or applying] *pre-made* metallic colloid or aggregate of nanoparticles" as recited in claims 22, 41 and 42. The Examiner is requested that she should not ignore the terms "positively charged" and "pre-made" as these limitations add meaningful limitations to the claims.

Claims 22-25 and 29 were rejected as being obvious over Bruchez in view of Van den Engh. This rejection is respectfully traversed.

Both Bruchez and Van den Engh fail to disclose "applying *pre-made* metallic colloid or aggregates of nanoparticles to the probe-target complex" as recited in claim 22. Again, the Examiner is requested that she should not ignore the limitation "pre-made" as this limitation adds meaningful limitation to claim 22.

Claims 33-34 were rejected as being obvious over Vo-Dinh in view of Isola. This rejection is respectfully traversed.

Both Vo-Dinh and Isola fail to disclose "a positively charged Raman signal enhancer, wherein the positively charged Raman signal enhancer" of claim 33 and "aggregating pre-made metallic colloid or aggregate of nanoparticles with said nucleic acid covalently attached to a positively charged Raman signal enhancer" of claim 43. The Examiner is requested that she should not ignore the terms "positively charged" and "pre-made" as these limitations add meaningful limitations to the claims.

Claim 12 was rejected as being obvious over Cao in view of Mirkin in view of Lane. This rejection is respectfully traversed.

Claim 12 depends from claim 1. Claim 12 should now be allowed as claim 1 should now be allowable. Also, Lane does not fill the gaps in Cao and Mirkin, stated above.

Claims 1, 5-11 and 14-17 were rejected as being obvious over Pastinen in view of Cao and Mirkin. This rejection is respectfully traversed and should be withdrawn as Pastinen fails fill the gaps in Cao and Mirkin as acknowledged by the Examiner during the interview of July 20, 2007.

Claims 22-27 were rejected as being obvious over Cao in view of Mirkin further in view of Bruchez and Van den Engh. This rejection is respectfully traversed.

All of Cao, Mirkin, Bruchez and Van den Engh fail to disclose "applying *pre-made* metallic colloid or aggregates of nanoparticles to the probe-target complex" as recited in claim 22.

Claim 28 was rejected as being obvious over Bruchez in view Van den Engh, further in view of Livak as evidenced by DNA from Wikipedia.com. This rejection is respectfully traversed.

Claim 28 depends from claim 22. Claim 28 should now be allowed as claim 22 should now be allowable. Also, Livak as evidenced by DNA from Wikipedia.com does not fill the gaps in Bruchez and Van den Engh, stated above.

Claims 30-32 were rejected as being obvious over Bruchez in view of Van den Engh, further in view of Chan.

Claims 30-32 depends from claim 22. Claims 30-32 should now be allowed as claim 22 should now be allowable. Also, Chan com does not fill the gaps in Bruchez and Van den Engh, stated above.

Claims 33-36 were rejected as being obvious over Mirkin in view of Vo-Dinh. This rejection is respectfully traversed.

Both Mirkin and Vo-Dinh fail to disclose "a positively charged Raman signal enhancer, wherein the positively charged Raman signal enhancer" recited in claim 33.

In light of this Amendment, a Notice of Allowance is respectfully solicited.

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